Remarks

Reconsideration of this Application is respectfully requested.

Claims 27-46 are pending in the application, with claims 27, 32, 37, and 43 being the independent claims.

Rejections Under 35 U.S.C. § 101

The Examiner has maintained his rejection of claims 27 - 46 under 35 U.S.C. § 101. According to the Examiner, based on the reasons set forth in Paper No. 5, the claimed invention is supported by neither a credible, substantial and specific asserted utility, nor a well-established utility. Applicants respectfully traverse the rejection.

The Examiner first refers Applicants to Example 12 of the *Revised Interim Utility Guidelines Training Materials* (the "Training Materials"). This example demonstrates the application of the Utility Guidelines in the context of a hypothetical protein that has been isolated from a cell membrane and has been shown to bind to "protein X." In this example, the protein is characterized by the applicant as "receptor A." The characterization of the protein as a receptor is based *solely on the fact that the protein was isolated from a cell membrane and that it binds to protein X*. Furthermore, the applicant in this example asserts two utilities for the claimed invention. First, a method of identifying materials which bind to the receptor, and second, a method of making a monoclonal antibody.

According to the Training Materials, implicit in the asserted utilities is the use of compounds to exert control over the action of the receptor in the treatment of a disease or condition. The Training Materials conclude that, although the asserted utilities are *specific*,

they are not *substantial*. The basis for this conclusion is that neither the applicant nor the art of record disclosed any diseases or conditions associated with receptor A.

The fact pattern set forth in Example 12 of the Training Materials is distinguishable from the disclosure and claims of the present application. First, as compared to the hypothetical disclosure of Example 12 (where the only evidence to suggest that the identified protein was a receptor was the fact that it was isolated from a cell membrane), Applicants have provided substantially more evidence that the claimed proteins are receptors and that they function in important physiological processes, namely apoptosis. This evidence is discussed in detail below.

Second, in Example 12 there was no evidence provided that the receptor was associated with any disease or condition. In contrast, Applicants in the present application have provided evidence that the claimed proteins are integrally involved in the process of apoptosis. As indicated in the present application and recognized by those skilled in the art at the time the present application was filed, disruption of the apoptotic machinery is associated with a variety of diseases and disorders. *See*, specification at page 3, lines 14-16 ("Derangements of apoptosis contribute to the pathogenesis of several human diseases including cancer, neurodegenerative disorders, and acquired immunodeficiency syndrome."); *See also* specification at page 38, line 18, to page 39, line 2 (describing various diseases associated with increased or decreased apoptosis).

Furthermore, Applicants' disclosure indicates that the present invention is useful for the treatment of diseases associated with de-regulated or abnormal apoptosis. *See*, specification at page 39, lines 3-19. Among such diseases specifically mentioned are cancers such as follicular lymphomas. *See*, specification at page 38, lines 18-19. Importantly, recent

results suggest a link between DR3 and follicular lymphoma. *See* Warzocha *et al.*, BIOCHEM. BIOPHYS. RES. COMMUN. 242:376-379 (1998) (copy enclosed). In this article, Warzocha and coworkers describe the isolation of an isoform of DR3 from mRNAs of a panel of human cell lines and tumor tissues obtained from patients with follicular non-Hodgkin's lymphoma. These results strongly suggest that DR3 functions to participate in lymphoid cell homeostasis. *See id.* at page 379 ("the 'programmed' change in DR3 alternative splicing may have functional effects not only in lymphocyte activation but also in lymphocyte differentiation and malignant transformation."). Therefore, unlike the disclosure described in Example 12, Applicants here have disclosed diseases and conditions associated with the claimed receptors and thus have defined a "real world context of use."

In summary, the fact pattern presented in Example 12 of the Training Materials is considerably different from the disclosure and circumstances surrounding the present application in terms of the utility requirement. Therefore, Applicants assert that the reasoning provided in Example 12 -- demonstrating why the utility requirement was not satisfied for the hypothetical protein described therein -- cannot be extended to the analysis of the utility of Applicants' claimed invention.

The Examiner has also rejected Applicants' assertion that the *substantial utility* prong of the Utility Guidelines is satisfied with respect to the proteins of the present invention. In pointing out Applicants' supposedly "misplaced" reliance on *In re Brana*, The Examiner states:

> The protein of the instant invention does not belong to a family of compounds with a common well established specific and substantial utility. The utility of those members of the receptor family to which the claimed protein in the instant application belongs lies in the knowledge that they modulate a specific physiological activity in response to a specific

> ligand. Since the instant specification does not disclose the identity of a native ligand for the claimed protein, a knowledge of the pathway through which that receptor transduces its signal in response to that ligand is not particularly useful.

Paper No. 6, page 2.

In the Examiner's view, the utility of a member of the TNF receptor family is dependent on the identification of a specific ligand that interacts with and activates the particular receptor. Applicants disagree with this position because the proteins of the present invention possess specific, substantial and credible utility, even if the identity of the ligand(s) that interacts with them are unknown.

For example, an antibody directed against the DR3 polypeptide may be used to treat diseases and disorders associated with decreased apoptosis. It is well known in the art that antibodies can agonize receptor proteins having death signaling activity in order to enhance apoptosis. *See*, specification, page 39, lines 3-11.

Further, in order to treat diseases and disorders associated with decreased apoptosis (caused, *e.g.*, by insufficient levels of DR3), the proteins of the claimed invention can be administered to a patient. *See, e.g.*, specification at page 29, lines 9-16:

> DR3-VI or DR3 polynucleotides and *polypeptides* may be used in accordance with the present invention for a variety of applications, particularly those that make use of the chemical and biological properties of DR3. Among these are applications in treatment of tumors, resistance to parasites, bacteria and viruses, to induce proliferation of T-cells, endothelial cells and certain hematopoietic cell, to treat restenosis, graft vs. host disease, to regulate anti-viral responses and to prevent certain autoimmune diseases after stimulation of DR3 by an agonist. (Emphasis added).

The use of the DR3 protein, independent of an identified ligand, is further demonstrated in Example 6 of the specification where high levels of DR3 in a cell -- simulating DR3 activation -- was shown to cause apoptosis (these results are discussed in more detail below). Thus, the claimed proteins possess sufficient utility under 35 U.S.C. § 101 regardless of whether the identity of the corresponding ligand is known or unknown.[2]

Finally, the Examiner appears to misconstrue Applicants' discussion of the cell death consequences that result from overexpression of the claimed proteins, as these consequences relate to the utility of the invention. The Examiner states:

> [T]he fact that a protein of the instant invention can cause cell death when overexpressed in a cell does not provide a specific and substantial utility since there appears to be no selectivity for this action which is disclosed in the instant specification as advantageous for a particular and practical purpose.

Paper No. 6, page 3. Furthermore, the Examiner asserts: "virtually any compound in sufficient concentration, including sodium chloride, water, and sucrose, will cause the death of a cell." *Id.*

The Examiner's statements are apparently based on a belief that cell death resulting from DR3 overexpression is a non-specific consequence of high protein levels within a cell and is unrelated to the properties of DR3 itself. This view, however, is contradicted by the evidence presented in the present application.

First, overexpressing TNF receptor family members has been shown to mimic receptor activation. *See*, specification at page 69, lines 20-21; *See also* Screaton *et al.*, PROC. NATL. ACAD. SCI. USA 94: 4615-4619, 4617 (1997) ("Overexpression of Fas or TNF-

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[2]Applicants note that a ligand for DR3 (also known as Apo3) was identified in 1998. *See* Marsters *et al.*, CURR. BIOL. 8:525-528 (1998) (copy enclosed).

R1 can lead to apoptosis in the absence of their ligands, probably through homomultimerization of the death domains.") (cited in the Information Disclosure Statement filed August 18, 1999). Accordingly, it is likely that the cellular consequences observed when DR3 is overexpressed are a reflection of the effects of DR3 activation -- not simply the deleterious results of too much protein in the cell. It is well understood in the art that *over*-expression refers to expression above background, in order to distinguish the activity of the expressed protein. Cells are commonly engineered recombinantly to overexpress proteins in order to make the proteins in a process where cells grow and not die.

Second, the cellular effects of DR3 overexpression, as disclosed in the present application, are indicative of *apoptosis* -- not merely *general cell death*. The cells in which DR3 was overexpressed "displayed morphological alterations typical of cells undergoing apoptosis, becoming rounded, condensed and detaching from the dish ... Nuclei of cells transfected with DR3, but not [a mutant version of DR3], exhibited apoptotic morphology as assessed by DAPI staining." Specification, page 71, line 25 to page 72, line 1. Apoptosis is described as "the highly orchestrated form of cell death in which cells neatly commit suicide by chopping themselves into membrane-packaged bits." Miller and Marx, SCIENCE 281:1301 (1998) (copy enclosed). This highly stereotyped form of programed cell death is readily distinguishable from the cell death (membrane lysis) resulting from a hypertonic concentration of sodium chloride or sucrose within a cell. Apoptosis is also distinguishable from mitotic inhibition that often results from high levels of protein that interfere with the cell division machinery.

Third, the Examiner's contention that the cell death caused by ectopic expression of DR3 is a non-specific consequence of high protein concentration is directly refuted by the

results described for the mutant version of DR3, "DDR3" (also known as "ΔDR3"). DDR3 is identical to DR3 except that it possesses a death domain mutation. *See*, specification at page 65, line 24. If the Examiner's position is correct, *i.e.*, that cell death is a function of high protein levels unrelated to the biochemical properties of DR3, one would expect that DDR3, as well as DR3, would result in cell death when ectopically expressed. However, as Example 6 demonstrates, ectopic expression of DDR3 *did not* result in the apoptotic consequences that were observed when DR3 was expressed. *See*, specification at page 71, line 28 - page 72, line 1. This proves that DR3 killing is dependent on its death domain and is not the result of high protein concentration.

Fourth, DR3-induced apoptosis was blocked when reagents were included that had been previously shown to inhibit apoptosis induced by the TNF receptor family members TNFR-1 and Fas/APO-1. *See*, specification at page 72, lines 3-7 ("DR3-induced apoptosis was blocked by the inhibitors of ICE-like proteases, CrmA and z-VAD-fmk [and by] dominant negative versions of FADD ... or FLICE"). Again, if the cell death observed when DR3 was ectopically expressed was merely the result of high protein levels then, contrary to what was actually observed, one would expect the addition of protease inhibitors to have no effect on DR3-induced cell death. The results described in the specification demonstrate that DR3-induced cell death is not caused by the general effects of high protein levels, but is the result of the highly coordinated biological process of apoptosis. Since apoptosis is a specific biological consequence directly associated with DR3, the claimed proteins of the instant application possess specific, substantial and credible utility.

In summary, Applicants reiterate their contention that the proteins of the present invention possess specific, substantial, and credible utilities. The claimed DR3 polypeptides

have been shown to induce apoptosis; Applicants, consistent with these results, assert that the claimed polypeptides are useful for, among other things, the treatment of diseases associated with "derangements of apoptosis." The asserted utilities are *specific* because the induction of apoptosis is specific to the claimed invention and is not applicable to the broad class of the invention (*i.e.*, not all receptors are involved with the process of apoptosis). In addition, the asserted utility is *substantial* because abnormal apoptosis is associated with a variety of diseases and conditions, and the claimed proteins can be used to treat such diseases. Finally, the asserted utility is *credible* because use of the claimed proteins to treat diseases associated with abnormal apoptotic properties would be believable to one skilled in the art. The results of Warzocha *et al.*, *supra*, implicating DR3 in follicular non-Hodgkin's lymphoma, confirm the credibility of Applicants' asserted utilities in this context.

In view of the arguments set out above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained his rejection of claims 27 - 46 under 35 U.S.C. § 112, first paragraph, as not being supported by either a credible, substantial and specific asserted utility or a well-established utility. *See* Paper No. 6, pages 3-4. Applicants respectfully disagree and note that this rejection has been sufficiently addressed above with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-46 under 35 U.S.C. § 112, first paragraph.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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